

Clinical Communications

A pediatric case of chronic idiopathic urticaria induced by antihistamines

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Clinical Implication

- Although oral antihistamines are considered first-line agents for the treatment of urticaria, in some cases antihistamines can precipitate the urticaria.

TO THE EDITOR:

A previously healthy 8-year old boy was seen for a second opinion regarding a 1-year history of urticaria. The initial onset of generalized urticaria was noted 30 minutes after a dose of fexofenadine for seasonal allergy symptoms. He had tolerated

fexofenadine in previous pollen seasons without any complications. Since onset, he has had daily generalized urticaria. After 2 months of symptoms despite taking daily fexofenadine (180 mg), the medication was changed to diphenhydramine 25 mg nightly. After 4 months without improvement, his medication was then changed to loratadine 5 mg twice daily, and his medication subsequently was changed to cetirizine 10 mg twice daily because symptoms remained unchanged. Although there was waxing and waning of severity, he had no days in which he was entirely symptom-free and had missed 19 days of school due to flares. Other than antihistamines, his only medication was montelukast for mild persistent asthma. Interestingly, since stopping cetirizine and montelukast for 3 days in anticipation of possible skin prick testing at the clinic, he did not have any urticaria.

The patient's urticaria occurred year-round, with no change in any particular season or time of day. His family reported that although he may have missed a day or two, he otherwise took an



FIGURE 1. The patient's chest before (*left*) and 1 hour after (*right*) oral challenge with 5 mg of cetirizine.



FIGURE 2. The patient's left arm before (*left*) and 6 hours after (*right*) oral challenge with 25 mg of diphenhydramine; a 12.5-mg dose of diphenhydramine was given 4 hours before this dose and had not produced any clinical symptoms.

antihistamine every day. He described seeing hives on awakening, but the hives did not cause night awakening. The hives were not triggered by heat, sunlight, cold, or pressure. He had no associated angioedema, fever, active joints, or constitutional symptoms. His physical examination revealed no skin lesions and was negative for dermatographism. Given the lack of lesions, the possibility that antihistamines were causing his symptoms was considered. His parents were instructed to have him continue avoiding antihistamines and to contact our office when his urticaria returned.

On follow-up 1 month later, the patient continued to be urticaria-free despite restarting montelukast and while not taking antihistamines. He agreed to an open oral challenge of 5 mg of cetirizine. After 30 minutes, he developed urticaria on the arms and chest, which progressed throughout the night (Figure 1). He had generalized urticaria the following morning. Topical hydrocortisone cream was applied, and the symptoms resolved after 24 hours. He did not develop any further urticaria.

Two months later, the patient remained urticaria-free, and agreed to an open challenge to diphenhydramine. He was given 12.5 mg of medication. Four hours later, no symptoms were seen; thus, a 25-mg dose was given. Six hours later, he awoke with urticaria on his arms and legs. The pruritus worsened over the next 4 hours before eventually resolving the next day (Figure 2).

Although antihistamines are widely used to treat urticaria, antihistamines themselves can trigger the disease. The mechanism is unknown, but the hypothesis includes metabolite haptenization¹⁻³ and nonimmune intolerance.⁴ A non-IgE-mediated mechanism may help explain the prolonged time between ingestion and appearance of urticaria in the patient's diphenhydramine challenge. Blinded, positive oral provocation testing has implicated multiple antihistamines from different classes: piperazines (cetirizine, levocetirizine, hydroxyzine), ethanolamines (diphenhydramine), alkylamines (dexchlorpheniramine), and piperidines (loratadine, desloratadine, fexofenadine, ebastine, azelastine, mizolastine, bepotastine, mequitazine).¹⁻⁴ Cetirizine has been most commonly cited as the urticaria-inducing antihistamine, with 7

reported blinded, provocation-proven cases.¹⁻⁴ Case reports also document urticaria induced by multiple antihistamines from different chemical classes with the same patient,^{1,2,4} as was demonstrated in the patient's history. Negative skin testing and patch testing have not been predictive of oral provocation outcome.²⁻⁴ To my knowledge, this is the first report of a pediatric case of urticaria induced by antihistamines.

This case teaches that when an antihistamine is ineffective for the treatment of chronic urticaria, it may be beneficial to remove such a medication sooner rather than later. For the majority of cases of chronic urticaria, the underlying cause remains unidentified, and patients have diminished quality of life for weeks to years. Consideration of urticaria induced by antihistamines is important because its identification and avoidance effectively resolves the disease.

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